REMARKS

Entry of the foregoing, reexamination and reconsideration of the application identified in caption, as amended, pursuant to and consistent with 37 C.F.R. §1.111 and in light of the remarks which follow, are respectfully requested.

In the present Amendment, claims 38, 39, 41, 43, 47 and 52 have been amended to change their dependency to claim 70. Claims 37, 53, 54, 68, 69, 78 and 79 have been canceled without prejudice or disclaimer. Claims 1-36 and 55-63 were previously canceled. No new matter has been added.

Upon entry of the Amendment, claims 38-52, 64-67, 70-77 and 80-95 will be all the claims pending in the application.

I. Response to Rejections under 35 U.S.C. § 103(a)

a. Claims 37, 38, 41-44, 47-54, 68-80 and 82-95 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,241,993 to Breton et al., in view of Robinson et al., *Contact Dermatitis*, "Evaluation of a quantitative clinical method for assessment of sensory skin irritation," 45:205-213, 2001, and Trevisani et al., *Nat. Neurosci.*, 2002, Jun; 5(6):546-551; e-publication date: 05/07/2002.)

b. Claim 81 was rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Breton et al. in view of Robinson et al., Trevisani et al., and further in view of Seidenari et al., *Contact Dermatitis*, 1998; 38(6):311-315, abstract only.

Applicants respectfully traverse the rejections for the following reasons.

Independent claims 70, 87 and 92 are directed to a method of evaluating the level of skin neurosensitivity of an adult individual to a capsaicinoid, comprising, *inter alia*, applying to a skin area of the individual a composition comprising a physiologically acceptable vehicle that is an aqueous or aqueous-alcoholic solution and a peripheral nervous system stimulant

that is a capsaicinoid, the concentration of the stimulant being between $1 \times 10^{-6}\%$ and $5 \times 10^{-4}\%$ (or $1 \times 10^{-4}\%$) by weight relative to the total weight of the composition.

One objective of the present invention is to further increase the diversity of models and devices available to the public for evaluating the skin sensitivity of an individual and provide a test allowing the determination of a sensitive skin population. Having sensitive skin is a permanent state characterized by sensitivity of skin to very low concentrations , such as $1 \times 10^{-6}\%$ and $5 \times 10^{-4}\%$ by weight, of a peripheral nervous system stimulant. Applicants advise that the studies regarding sensitive skin have shown that the threshold of sensitivity of the skin was very low, e.g., less than 1.10 - 3%.

The present specification demonstrates the importance of the presently recited concentrations of peripheral nervous system stimulant in evaluating the level of skin neurosensitivity. For example, as described in paragraph [0116] of the present specification, the subjects who detected $3.16 \times 10^{-5}\%$ (C1), $1 \times 10^{-4}\%$ (C2) and $3.16 \times 10^{-4}\%$ (C3) form a "sensitive to highly sensitive" population, and the subjects who detected $1 \times 10^{-3}\%$ (C4) and $3.16 \times 10^{-3}\%$ (C5) and who did not detect any concentration form a "virtually or completely insensitive" population (see, also, Fig. 6; paragraph [0101]). Therefore, using a concentration of $1 \times 10^{-3}\%$ or higher would not allow the determination of a sensitive skin population or the evaluation of the level of skin neurosensitivity.

In addition, the recited concentration of the peripheral nervous system stimulant is critical because when using more concentrated solutions, the test may lead to false positive results. For example, when subjected to a test using a peripheral nervous system stimulant with a higher concentration, an individual who does not have sensitive skin may be caused to feel unpleasant sensation, thereby leading to false positive results.

Furthermore, as described in an article entitled "Detection Thresholds of Capsaicin: A New Test to Assess Facial Skin Neurosensitivity," by Roland JOURDAIN et al. J. Cosmet. Sci., 56, 153-156 (May/June 2005), which is partially authored by the present inventors and a copy of which has previously been submitted on September 28, 2007, using relatively low concentrations of capsaicine, such as those defined in the present claims, can allow the detection of sensitivity, which is not dependent upon subject's appreciation.

Moreover, the use of low concentrations of peripheral nervous system stimulant, such as capsaicine, as recited in the present claims, allows use of a lower concentration of physiologically acceptable vehicle, such as ethanol. As such, the test can be applied on the face of an individual.

Breton et al. discloses the same test as EP 0 680 749 cited in the present specification (paragraph [0025]). Specifically, EP '749 describes a test with capsaicin for characterizing people with sensitive skin by virtue of the neuro-sensorial response induced by cutaneous application of capsaicin. Persons with sensitive skin show, in effect, levels of skin discomfort which are greater than in those having non-sensitive skin following application of a capsaicin cream. This test consists of applying to approximately 4 cm^2 of skin 0.05 ml of a cream containing 7.5×10^{-2} % of capsaicin and recording the appearance of subjective signs provoked by this application, such as stinging, burning and itching. In contrast to the lactic acid test, this test has a predictive character for the diagnosis of sensitive skin. The specification continues in paragraphs [0026] and [0027] that:

> The test takes a long time to implement (approximately 30 minutes) and cannot be used in practice, simply, by consumers for self-diagnosis of their own sensitive skin. Moreover, the test described in EP '749 necessarily involves using a cream of which the amount to be applied must be quantified using a 1 ml syringe, and the application of the cream over a very precise area of the skin. In fact, the practical performance of this test necessitates the presence of an experimental technician to perform the test on a person.

> The protocol of the test of EP '749 is therefore difficult to implement by an unskilled person, and consequently it is particularly unsuitable for use by a consumer in self-diagnosis.

On the other hand, by using the presently claimed invention, the waiting time after the application of the composition will not be more than 360 seconds; this is very short compared to the estimated longest waiting time of 20 minutes of the test disclosed in Breton et al. The maximum test duration of the presently claimed method is 20 to 25 minutes for subjects continuing through to the final step of the test (see paragraph [0093] of the present specification), whereas the second step of the method disclosed by Breton et al. alone can take 20 minutes. The presently claimed method is thus shorter to implement than the method of Breton et al.

Furthermore, as noted above, the test disclosed in Breton et al. cannot be used in practice, simply, by consumers for self-diagnosis of their own sensitive skin. The quantification of the cream necessitates the use of a 1 ml syringe and the application of the cream in a precise area of the skin (4 cm^2) so the practical performance of this test on a person necessitates the presence of an experimental technician. In contrast, the presently claimed method can be fully performed by a consumer himself.

Lastly, Breton et al.'s test can induce painful sensations because of the single dose applied on the skin and, particularly in subjects with a very sensitive skin or in Chinese population (see Jourdan et al., mentioned above and previously submitted). In contrast, the presently claimed method will be totally painless.

As such, Breton et al. does not provide a simple, quick and painless method for evaluating the level of neurosensitity of an adult individual.

The Office Action concedes that Breton et al. fails to teach that the capsaicin is in an aqueous or aqueous-alcoholic solution, the concentration of the capsaicin, the specific skin area to be tested, that the concentration of capsaicin is increased until an individual detects the stimulant, or that the aqueous-alcoholic solution contains a certain percentage of ethanol in water.

i. There is no apparent reason to combine Breton et al. and Trevisani et al.

Trevisani et al. discloses that ethanol can potentiate the response of VRI, a receptor for noxious heat, to capsaicin and thus leads to neuropeptide release and plasma extravasion.

To measure the plasma extrasavation, Trevisani et al. used some anesthetized rats and injected capsaicin (1mM) or ethanol in their esophageous via a cannula inserted into the oral part of the esophageous. This way of administering capsaicin or alcohol is totally different from the topical application and the capsaicin amount is 1000 times higher than the highest amount in the presently claimed range. As such, one of ordinary skill in the art would not have had an apparent reason to combine Breton et al. and Trevisani et al., in the manner proposed in the Office Action.

ii. The combination of Breton et al., Trevisani et al., Robinson et al. and Seidenari et al. would not result in the subject matter recited in present claims 70, 87 and 92

In Trevisani et al.'s study was tested the response to ethanol and/or to capsaicin of various tissues samples (thick slices of the dorsal horn of lumbar enlargements of the dorsal spinal cord, oesophagus and skin from the shaved dorsum of rats) and of several kinds of cells: hVR1-expressing or wild-type HEK293 cells (i.e., human embryonic kidney cells), human hepatoma (Hep G2) cells and primary neurons from trigeminal and dorsal root ganglia (DRG and TGN). The amount of capsaicin used, in vitro, on these biological materials (from 0.1 nM to 10 μM) cannot be extrapolated to a topical use of capsaicin on a skin area of an

adult individual. Due to biodisponibility matter, one skilled in the art would automatically think that these amounts have to be re-evaluated for their in-vivo use.

In the presently claimed invention, the range of amounts is determined in order to be painless but efficient to obtain the thresholds of detection of capsaicin of individuals. With the tissues and cells used in Trevisani et al.'s study, it is not possible to assess if these amounts are painful or painless and what are the thresholds of detection.

Further, the presently claimed invention employs a precise range of capsaicin amounts which allows to grade individuals in term of skin sensitivity and to use this range in a painless and accurate method. On the other hand, assuming, *arguendo*, one skilled in the art decides to take the amounts disclosed in Trevisani et al., he can have not less than three different situations as follows:

- If the amount used is from 0.1 nM to 0.19 μM (i.e., 1×10^{-6} % = lowest amount of the presently claimed range), this amount will not be efficient to determine a threshold of detection of capsaicin. Many individuals having a sensitive skin will not be thus identified and the gradation will be wrong.

- If the amount used is from 0.19 μM to 10 μM, this amount will be inside the range recited in the present claims.

- Because one skilled in the art will not use capsaicin at an amount from 10 μM to 95 μM (i.e., 5×10^{4} % = highest amount of the presently claimed range), many tested individuals will not be classified as having a sensitive skin. Thus, the gradation will be wrong.

This can prove that, for a skilled person, the range of capsaicin amounts for use was not so obvious to determine. The sole determination of the lowest detectable range of capsaicin concentrate is not enough to better differentiate individuals having "sensitive" skin from the others. The selection of the precise range recited in the present claims cannot be

considered as an obvious optimization because one skilled in the art will have to test amounts varying from 0.1 nM to 10 μM and will have a probability of 90% to not achieve the invention given the very limited range recited in the present claims.

As such, the teaching of Trevisani et al. would not lead a skilled person to evaluate skin neurosensitivity of individuals by topically using a specific range of amounts of capsaicin.

Robinson et al. aims to the development of "better methods for predictive testing and risk assessment" of dermatological products and standard tests for the evaluation of irritant potential of new topical ingredients or products. It is clear throughout the article that individual subjects were tested regardless the sensitivity of their skin. The purpose of Robinson et al. is to characterize a product and not a population of subjects. Robinson et al. concludes that the "use of recall/imagined skin sensation perception data for prediction of actual reactivity to chemical probes may have screening utility depending on the survey questions used" (see, Abstract).

Particularly, Robinson et al. describes studies related to response of individual subjects to a topical application of chemosensory irritant chemicals using the labeled magnitude (LM) scale, for pre-market dermatotoxicologic safety testing and risk assessment (page 211, paragraph bridging left and right column).

The capsaicin treatment studies in Robinson et al. were performed by using capsaicin in 80% ethanol at concentrations of 100 to 10,000 mM (page 206, right column, first paragraph), which correspond to 3.12×10^{-3}% to 3.12×10^{-1}% by weight and thus fall outside the ranges recited in present claims 70, 87 and 92. In addition, Robinson et al. does not disclose or suggest the above noted unexpected results achievable by using capsaicin solutions with concentrations between 1×10^{-6}% and 5×10^{-4}% by weight.

Further, Robinson et al. describes in one part of the study, intensities of self-assessed sensations and of experimental application of chemicals are compared. Specifically, the study procedure consists of (i) questioning subjects on the intensity of recalled/imagined sensations when testing these subjects with a product; and then (ii) identifying the degree of correlation between self-perceived reactivity to recall/imagined skin stimuli and actual measured chemosensory responses.

Robinson et al. further states that "the results of the capsaicin study showed some degree of correlation between self-perceived 'reactivity' to recall/imagined skin stimuli and actual measured chemosensory responses" (page 210, right column, third paragraph; page 212, right column, first paragraph). However, the conclusion of this part of the study is that no consistency exists between the intensity of the recalled/imagined sensations and the actual measured chemosensory reactivity after applying a product (see page 210 and Fig. 7). That is, there is no clear pattern of answers or correlation between these answers and cutaneous reaction of tested individuals.

Specifically, Fig. 7 of Robinson et al. shows the non-absolute correlation between self-perceived "reactivity" to imagined skin stimuli and actual measured chemosensory response. The method disclosed in Robinson et al. clearly allows to divide the population in two groups; however, it does not allow to precisely grade subjects according to their skin neurosensitivity. The biggest group comprises subjects with high self reactivity to recall skin sensations and who perceive a moderate sensation to capsaicin amounts not higher than 1000 μM (i.e., 3.2×10^{-2} %). That is, this group will comprise subjects having a sensitive skin. The other group comprises some subjects with a low or a high self reactivity to recall skin sensations and who perceive a moderate sensation to capsaicin amounts higher than 1000 μM. That is, this group will comprise subjects declaring that they have or do not have a

sensitive skin. It clearly means that this method cannot be used to achieve precise gradation of subjects according to their skin sensitivity because the global results will be spoiled by false-positive results (almost 50% of the subjects of the second group). The accurate gradation of subjects according to threshold dose of capsaicin while the tested doses range between 100 and 10000 μM is thus not possible. Robinson et al. does not disclose this problem of false-positive results.

Concerning another part of the study in Robinson et al., considerable variability between individual subjects was found when testing with capsaicine, even across the range of skin sensations described.

In view of the descriptions in Robinson et al. as a whole, one of ordinary skill in the art would rather have been taught away from using capsaicine to elaborate a method to classify one population, e.g., concerned with sensitive skin. Indeed, variability between individual subjects has to be avoided to achieve a reliable method to evaluate the level of skin neurosensitivity.

Moreover, Robinson et al. does not address the issue of sensitive skin. Furthermore, Robinson et al. does not correlate high reactivity to a peripheral nervous system stimulant to sensitive skin. Thus, it would not have been obvious to a skilled artisan to try to vary a peripheral nervous system stimulant dose allowing the identification of sensitive skin, and particularly, to reduce the stimulant dose to identify a person with sensitive skin.

Lastly, in the presently claimed invention, the information regarding the skin reactivity or sensitivity of the individual is deduced as a function of specific unattractive sensations which are not specifically targeted in the method of Robinson et al. (see page 207, column 1, line 4). The subjects are using the LM scale which merely evaluates the intensity of a sensation.

Seidenari et al. is cited against dependent claim 81 merely for the disclosure of a sting test including applying an irritant to the nasolabial fold.

As none of Robinson et al., Trevisani et al., and Seidenari et al., rectifies the above noted deficiencies of Breton et al., the combination of Breton et al., Robinson et al., Trevisani et al., and Seidenari et al would not result in the subject matter of claims 70, 87 and 92.

In view of the foregoing, Applicants respectfully submit that claims 70, 87 and 92 as well as dependent claims 38-52, 64-67, 71-77, 80-86 and 88-95 are patentable over Breton et al. in view of Robinson et al. and Trevisani et al., and further in view of Seidenari et al., and thus the rejections should be withdrawn.

II. Conclusion

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited. If there are any questions concerning this paper or the application in general, the Examiner is invited to telephone the undersigned at her earliest convenience.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

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